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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/295,925	Applicant(s) Joshi et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 27, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above, claim(s) *13-45* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12 and 46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2003, paper number 29, has been entered.

DETAILED ACTION

This application filed April 21, 1999 claims benefit to provisional applications: 60/028,665, filed April 22, 1998; 60/111,653, filed December 9, 1998; and 60/111,637, filed December 9, 1998.

Applicants' amendment filed February 27, 2003, paper number 30, has been received and entered. Claims 1-5 and 10-12 have been amended. Claims 1-46 are pending.

Election/Restriction

Applicants' election of Group I made March 9, 2000, paper number 9, was made with traverse. For the reasons set forth in the previous office action mailed April 24, 2002, the restriction is found proper and made FINAL (paper number 23, pages 3-4).

Claims 1-46 are pending. Claim 13-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. Claims 1-12 and 46 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). In the instant case, the claims have been amended to recite the term "high energy" electromagnetic radiation, however "high energy" is not recited or generally defined in the instant specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of "high energy radiation" is considered new matter.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-5, 11 and 12 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed,

involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Applicant argues that an application may be amended to recite an inherent property without introducing prohibited new matter, citing MPEP 2163.07(a) for support. Applicant argues that high energy radiation is well known in the art and has provided a textbook reference by Serways and point to Bolognia *et al.* to support that ultraviolet radiation is also considered a high energy radiation. See Applicant's amendment page 4, section 2. Applicant's arguments have been fully considered but not found persuasive.

Examiner acknowledges that electromagnetic radiation is recognized in the art to be represented by a spectrum as exemplified by Serway. However, it is noted that Serway does not use the term "high energy" radiation or indicate which part of the spectrum of electromagnetic radiation would be encompassed by this term either in types of radiation, as specific frequencies or specific wavelengths (see figure 34.17 for example). Again, Serway does teach that the various forms of radiation are part of a spectrum, but does not teach nor indicate that the art or the skilled artisan provides for a definitive range which would be considered "higher energy". For example, Giancoli, another textbook reference, provides a similar general description of

electromagnetic radiation and provides representative spectrums which are different from that of Serway (see page 579, figure 22-10). The specification teaches specific forms of radiation such as gamma rays, x-rays and ultraviolet rays, however it does not specifically define these as the forms of high energy electromagnetic radiation, nor conversely does the specification specifically define what is encompassed by the term "high energy" radiation. MPEP 2163.07(a) states "By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it." and that "The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter." However, unlike the examples provided in the cited case law (see *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA1973); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)), gamma rays, x-rays or ultraviolet rays are not products which specifically define the metes and bounds of high energy radiation nor does high energy radiation specifically define any one of the individual forms of radiation. Additionally, as presently recited in the claim "contacting said cells with high energy" radiation would be considered a product itself, not a definition or description of an inherent property. Further, it is noted that high energy radiation and the forms of specific radiation; gamma rays, x-rays or ultraviolet rays, are not equivalent or interchangeable terms. Even if one were to concede that gamma rays, x-rays or ultraviolet rays may be considered different forms of high energy radiation, they are not products the artisan

would consider to posses completely the broadness of this term. The term "high energy" electromagnetic radiation is a term not specifically recited nor defined in the present specification, and encompasses a particular breadth not specifically contemplated nor disclosed. Therefore, the amendment to the claims to recite "high energy" is considered new matter.

Claims 1-12 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, two points are at issue: (1) the required teaching and ability to use electromagnetic radiation to synchronize 30% of a population of cells; and (2) the required teaching and ability to synchronize said cells in any phase of the cell cycle besides G_2/M. It is noted that claim 1 has been newly amended to recite that synchronizing the cells through the use of electromagnetic radiation must result in "synchronizing at least 30% of said cells at a first stage of the cell cycle". The specification provides the general guidance for administering radiation to synchronize cells (bridging pages 20-21), however relies on the art for providing the specific methodology to practice the full breadth encompassed by the claims, in particular the specific devices and amounts the artisan can or must deliver. The specification provides one working example in which x-rays were used in mice to access whether the *in vivo* practice will result in increased transfection efficiency, however in this example the amount of cells which were synchronized was not measured. It is well established in the art that electromagnetic radiation that alter the DNA of a cell, such as x-ray and γ-ray radiation, can cause the cell to stop cycling at specific cell cycle check point until the damaged DNA is repaired. However, a limitation to this is providing a dose radiation which will not kill the cell instead of synchronizing. Spang-Thomsen *et al.* teach that irradiation causes a change in the proliferation kinetics of cells (see summary in abstract). More specifically, Spang-Thomsen *et al.* teach that

the treatment results in the synchronization of a small portion of cells, and that it is generally in a dose dependent manner (page 849, second column). However, the maximum percentage of synchronized cells obtained by Spang-Thomsen *et al.* is only 20% (page 851, middle of first column and figure 1). Importantly, Spang-Thomsen *et al.* teach that larger doses of radiation "result in a large fraction of radiation-induced necrotic cells" (page 851, bottom of first column). Therefore, even with increasing doses of radiation, the art teaches that a maximum number of cells which can be synchronized is 20% before the increasing radiation results in killing a large fraction of the cells. The instant specification provides no specific conditions for administering radiation wherein said conditions result in 30% of the cells becoming synchronized, and relies on the teaching and the knowledge present in the art to practice the claimed invention. Spang-Thomsen *et al.* teach that the maximum number of cells which are synchronized by x-rays is 20% and that increasing doses of radiation result in increasing necrotic cell death. Again the specification relies on the art for the administration of radiation to practice the claimed method, and provides no specific guidance to overcome any limitation which may present in the art. Given the evidence of Spang-Thomsen *et al.* that increasing amounts of radiation do not simply result in increasing number of synchronized cells, rather these conventional methods known in the art result in increasing cell death, and absence of any specific teaching in the instant specification for providing a solution to this art recognized problem, the specification fails to provide the required teaching and necessary guidance to overcome art recognized problems to practice the methods as instantly claimed.

With respect to using electromagnetic radiation to synchronize cells in any phase of the cell cycle besides G_2/M, it is well known in the art that high energy radiation can penetrate far into a cell or a subject *in vivo*, and through the mechanisms of DNA damage repair the cells become synchronized during the repair process, in particularly at the G2/M stage of the cell cycle (Spang-Thomsen *et al.*, page 849, second column). Presently, the claims encompass synchronization at any point in the cell cycle. In the instant case the mechanism of synchronization is important, because it is well accepted in the art that ionizing radiation such as x-rays and gamma rays, synchronizes the cell by virtue of DNA damage and damage repair mechanisms of the cell. The instant specification fails to provide the necessary guidance or demonstrate by example that cells can be synchronized at any other points in the cell cycle by electromagnetic radiation other than G2/M. The instant specification and the art of record fails to provide the nexus between synchronizing cells at G2/M with high energy radiation and the ability to synchronize the cell at other parts of the cell cycle with the same radiation or any other form of radiation encompassed by the claims. As discussed above, the instant specification relies on the art for the methodology of administering the radiation, and the specification is silent with respect to specific guidance or examples which demonstrate that the cell can be synchronized with high energy radiation in any other state than G2/M. Beyond the breadth of the claims encompassing synchronizing the cell to any part of the cell cycle, for claims 3 and 5, given the evidence of record it is unclear how a source of electromagnetic radiation can synchronize the cell at these specific points of the cell cycle.

In summary, the claimed invention is broad and encompasses the use electromagnetic radiation to synchronize 30% of a population of cells and the ability to synchronize said cells in any phase of the cell cycle besides G_2/M. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. In this case, the specification fails to provide the necessary guidance to practice the invention as claimed. Given the limitations taught in the art for the use of radiation to synchronize greater than 20% of a cell population and then only into the G_2/M check-point, the reliance on the art to practice the claimed methods, and the silence of the specification to overcome the art recognized problems, it would constitute undue amount experimentation without any expectation of success to practice the methods as claimed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 1-5 have been amended to recite that high energy radiation

is used, however the specification does not specifically recite or define the term "high energy radiation" and the metes and bounds of the claim are unclear because the spectrum of radiation encompassed by this term are not clearly set forth. Radiation is described as a spectrum (see for example Serway supplied by Applicant as attachment to the instant amendment) and absent specific definitions of a general term the specific boundaries and forms of radiation encompassed by this term and the claim is not specifically or clearly defined. Dependent claims 6-10, 46 are included in the basis of the rejection because they fail to further clarify the specific basis of the rejection. Claims 11 and 12 are not included in the basis of the rejection because though the claims recite "high energy" radiation, the claims define the radiation as the specific forms of gamma rays, x-rays or ultraviolet rays.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 12 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* in view of Spang-Thomsen *et al.* is withdrawn.

Claim 10 rejected under 35 U.S.C. 103(a) as being unpatentable over Yorifuji *et al.* in view of Spang-Thomsen *et al.* as applied to claims 1-9, 11,12 and 46 above, and further in view of Son *et al.* is withdrawn.

For each rejection, the amendment to the claims to encompass methods wherein "at least 30% of said cells" are synchronized by electromagnetic radiation has differentiated the claimed method from that taught in the prior art. In particular, Spang-Thomsen *et al.* provide the methodology to use x-ray radiation to induce the partial synchronization of cells, however the maximum level of synchronization obtained by Spang-Thomsen *et al.* through the use of radiation is only 20% (see summary of results in figure 1). The 20% maximum is seen at each amount of radiation used so there is no expectation that using more radiation would unexpectedly result in greater synchronization, in particular the at least 30% recited and required by the instantly claimed method.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to teach method steps wherein at least 30% of cells are synchronized by electromagnetic radiation, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach